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Award Number: DAMD17-00-1-0548

TITLE: Magnetic Resonance Spectroscopy Imaging and Function
Magnetic Resonance Imaging of Neurofibromatosis Type I: In vivo
Pathophysiology, Brain-Behavior Relationships and Reading
Disabilities

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REPORT DATE: March 2005

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGEForm Approved
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY		2. REPORT DATE March 2005	3. REPORT TYPE AND DATES COVERED Final (1 Oct 2000 - 31 Jan 2005)	
4. TITLE AND SUBTITLE Magnetic Resonance Spectroscopy Imaging and Function Magnetic Resonance Imaging of Neurofibromatosis Type I: In vivo Pathophysiology, Brain-Behavior Relationships and Reading Disabilities			5. FUNDING NUMBERS DAMD17-00-1-0548	
6. AUTHOR(S) Laurie E. Cutting, Ph.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Kennedy Krieger Institute Baltimore, MD 21205 E-Mail: cutting@kennedykrieger.org			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES Original contains color plates: ALL DTIC reproductions will be in black and white				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 Words) The purpose of this research is oriented towards understanding the reading, language, and articulation deficits associated with Neurofibromatosis Type 1 (NF-1) and relating these deficits to the underlying pathophysiology of NF-1 as revealed by Magnetic Resonance Spectroscopy Imaging (MRSI). A second goal is to determine how differences in activation, as measured by functional Magnetic Resonance Imaging (fMRI), are linked to the cognitive/academic impairments associated with NF-1. A third goal is to further understand how T-2 weighted hyperintensities on Magnetic Resonance Imaging (MRI) scans are related to cognitive/academic impairments associated with NF-1. Each aim addresses the research in terms of pathophysiology and how cognitive/academic functioning of children with NF-1 compares to control groups when examined in both genetic (i.e., sibling) as well as general population (both reading disabled and non-reading disabled) contexts. We hypothesize that abnormalities of NAA, Choline, or their ratios, will exist in the thalamus and will correlate with language, reading, and articulation deficits in NF-1, defined by "lowering" of the cognitive scores of each child with NF-1 relative to his/her unaffected sibling. For the second goal, we hypothesize that children with NF-1 will activate their brains similarly to reading disabled children during fMRI tasks. For the third goal, we hypothesize that reading, language, and articulation deficits will correlate with the number of brain locations with T2-weighted hyperintensities. Thus, neuroimaging permits the pursuit of furthering our understanding of how the NF-1 gene affects the brain in terms of basic neurobiologic factors (ultrastructural, physiological, and localization) as well as their impacts on cognition (reading, language, and articulation) in NF-1.				
14. SUBJECT TERMS Learning Disability Diagnosis, Neurofibromatosis Type 1, functional Magnetic Resonance Imaging, anatomical Magnetic Resonance Imaging, Magnetic Resonance Spectroscopy Imaging, Reading and Speech/Language Disorder			15. NUMBER OF PAGES 12	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

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INTRODUCTION

The purpose of this research is primarily oriented towards understanding and documenting the reading, language, and articulation deficits associated with Neurofibromatosis Type 1 (NF-1) and relating these deficits to the underlying pathophysiology of NF-1 as revealed by Magnetic Resonance Spectroscopy Imaging (MRSI). A second goal is to determine how differences in activation, as measured by functional Magnetic Resonance Imaging (fMRI), are linked to the cognitive and academic impairments associated with NF-1. A third goal is to further understand how the brain's visible abnormalities, T-2 weighted hyperintensities on Magnetic Resonance Imaging (MRI) scans, are related to the reading, language, and articulation deficits in NF-1. Each of the specific aims of the research addresses components of the research in terms of pathophysiology and how cognitive/academic functioning of children with NF-1 compares to control groups when examined in both genetic (i.e., sibling) as well as general population (both reading disabled and non-reading disabled) contexts. Based upon previous research findings, we hypothesize that abnormalities of NAA, Choline, or their ratios, will exist in the thalamus; further, that thalamic abnormalities will correlate with language, reading, and articulation deficits in NF-1, as defined by the "lowering" of the cognitive score of each child with NF-1 relative to that of his/her unaffected sibling. In terms of the second goal of this research, we hypothesize that children with NF-1 will activate their brains similarly to reading disabled children during fMRI tasks. In terms of the third goal of this research, we hypothesize that reading, language, and articulation deficits will (as reported for IQ) correlate with the number of brain locations in which T2-weighted hyperintensities are seen. Thus, the use of MRI, MRSI, and fMRI methodology in this research permits the pursuit of further understanding the basic neurobiologic factors (ultrastructural, physiological, and localization) as well as their impacts on cognition (reading, language, and articulation) in NF-1, thus furthering our understanding of how the NF-1 gene affects the brain.

BODY

Research Accomplishments Associated With Each Task: Tasks 1 and 2, which were targeted for years one and two of the grant, were continued to be addressed during the third and fourth years of the grant. Task 1 dealt with subject recruitment and data collection (targeted for months 1-26), and included the goals of recruiting patients for participation, screening patients for eligibility, and conducting onsite neuropsychological evaluations and MRSI/fMRI procedures. We have seen a total of 121 patients for the entirety of the grant (53 since the last report 10/31/2003; see chart below). Task 2 dealt with analyzing MRI data and scoring neuropsychological tests (months 3-26). We have analyzed MRSI data and fMRI data, and have also scored all the neuropsychological tests (including inter-rater reliability) that we administered.

Tasks 3 and 4 (data entry, statistical analysis, and results/manuscript preparation), which were targeted for the end of year 2 and all of year 3, were addressed in the final year of the grant as well. We continued to enter MRI and neuropsychological data into the database as we collected the MRI and neuropsychological data. In addition, we presented MRI findings and

neuropsychological findings at the *International Neuropsychological* meetings in February 2004 and February 2005 (Cutting, Clements, Schafer, Mostofsky, Pekar, & Denckla, 2004; Cutting, Clements, Schafer, Pekar, Mostofsky, Denckla, 2005; Clements, Cutting, Schafer, Pekar, Mostofsky, 2005; Rimrodt, Lightman, Abel, Denckla, & Cutting, 2005; Rimrodt, Lightman, Roberts, Denckla, & Cutting, 2005). We are also currently preparing manuscripts for publication on our neuropsychological and fMRI findings. In addition, we published an article on learning disabilities in NF-1 for a special issue of *Learning Disabilities Research and Practice* (Cutting, Clements, Lightman, Yerby-Hammack, & Denckla, 2004) and will be presenting findings to the *Society for the Scientific Study of Reading* conference in June, 2005 (Cutting & Scarborough, 2005). During the 4th year of the grant, in addition to the MRI and neuropsychological data collection, we focused on analyzing data manuscript preparation and presentation of findings.

Number of Patients Seen: During the third and fourth years of the grant, we saw 53 children altogether, 38 of which met criteria for inclusion in the study. Three children were determined ineligible because of an IQ below 80. Eleven had reading scores than fell inbetween reading disability (RD) and control criteria, and one had such significant difficulties with reading that he/she could not complete the rest of the testing. For those children who were found to be ineligible for the study, it did not present a problem because all of them participated in the testing and the parents received appropriate feedback (i.e., they will not be included in data analyses). Below is a chart of the participants:

	3 rd & 4 th YEARS	Total Eligible From All Four Years*
NF-1 W/OUT SIBLING	5	11
NF-1 W/SIBLING	3	7
NF-1 SIBLING (NON AFFECTED)	3	7
CONTROLS	17	45
READING DISABILITIES	10	23
TOTAL NUMBER SEEN:	39	93

*Note: We saw 121 patients, but only 93 met eligibility criteria.

Preliminary Findings/Progress:

MRI Findings: Data from the MRSI scans that we have collected have been analyzed by Dr. Barker's group. For the fMRI component of the grant, we collected data on 39 children for the visuospatial and phonological (reading) fMRI tasks. Below are results for the phonological task (rhyme) and the visuospatial task (analogous to the Judgment of Line Orientation; JLO; Cutting, Clements, Schafer, Pekar, Mostofsky, Denckla, 2005).

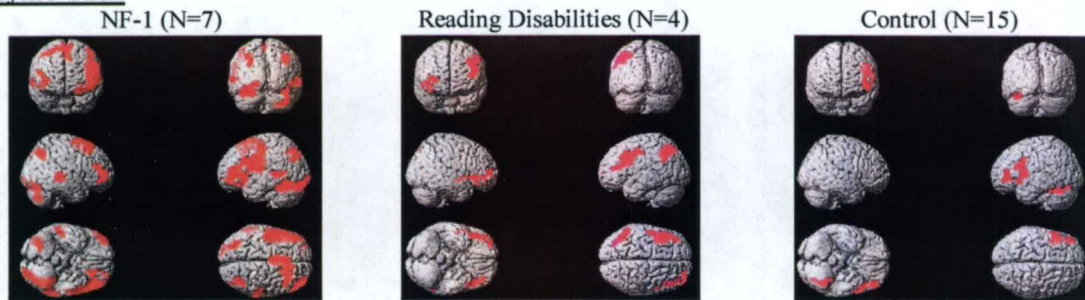
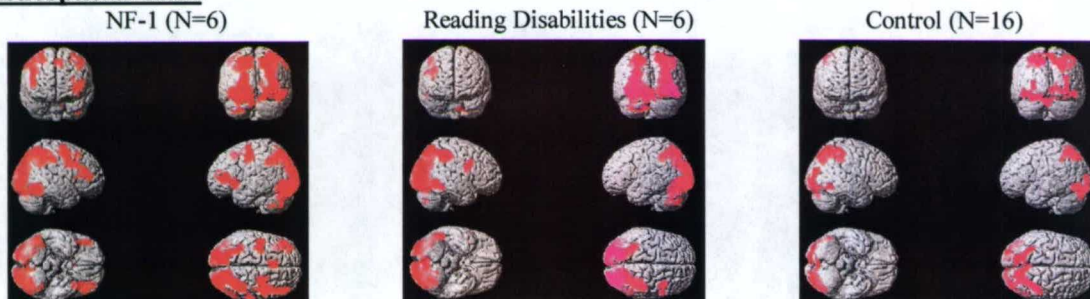
Rhyme Task**Visuospatial Task**

Figure 1. Maps Showing Activation Patterns during Rhyme and Judgment of Line Task (JLO) Tasks.

For the Rhyme task, the control group showed activation in left frontal and cerebellar areas. The NF-1 group showed activation in bilateral frontal and occipital lobes, and some activation in temporal lobes bilaterally. The RD group showed bilateral frontal activation (L>R) and left parietal lobe and cerebellar activation, with minimal occipital and temporal lobe activation.

For the JLO task, the control group showed bilateral occipital lobe (extending into inferior temporal lobes), parietal lobe, and cerebellar activation. The NF-1 group also showed bilateral occipital lobe (extending into inferior temporal lobes), parietal lobe, and cerebellar activation, but showed bilateral frontal lobe activation as well. The RD group showed bilateral parietal lobe, occipital lobe, and cerebellar activation.

Neuropsychological Findings: Cutting, Koth, David, & Denckla (2003) compared children with NF-1, controls, and children with RD on a variety of neuropsychological tests. Results show that children with NF-1 have similar deficits to children with RD. Multiple Analyses of Variance (MANOVAs) suggest that children with NF-1 have similar difficulties as children with RD, with both groups showing weaknesses in reading accuracy (decoding), reading comprehension, receptive and expressive language, and some aspects of figurative language. On the other hand, children with NF-1 appear to have some notable differences from children with RD. Unlike children with RD, results suggest that some aspects of inferential language and rate of retrieval (Rapid Naming) are relatively spared in children with NF-1. These findings suggest that intervention for the associated learning disabilities in children with NF-1 could be able to be tailored to this pattern of strengths and weaknesses (e.g., using their strong rate of retrieval abilities to help remediate language disabilities). Results are listed in Table 1:

Table 1			NF-1	RD	Controls
Ability Test		FSIQ	101.25 ± 17.98 †	100.30 ± 11.13 †	116.07 ± 14.35
		VIQ	103.58 ± 16.74 †	99.30 ± 15.85 †	119.13 ± 15.68
		PIQ	98.75 ± 18.39	102.30 ± 10.73	109.80 ± 15.02
Reading Tests	WIAT	Basic Reading	97.92 ± 11.71 †	83.80 ± 5.49 † ‡	117.20 ± 11.05
		Reading Comprehension	99.58 ± 11.59 †	93.60 ± 11.54 †	115.67 ± 11.95
	WJR	Word Attack	93.92 ± 14.77 †	82.40 ± 7.47 † ‡	115.87 ± 15.28
	GORT-3	Rate	10.75 ± 3.47 †	6.20 ± 2.35 † ‡	14.00 ± 3.98
		Accuracy	8.58 ± 3.06 †	7.10 ± 2.89 †	13.33 ± 3.33
Reading-Related Tests	CTOPP	Comprehension	10.00 ± 3.54 †	6.60 ± 2.84 † ‡	13.27 ± 2.69
		Phonological Awareness	93.00 ± 13.13	92.50 ± 13.87	105.60 ± 12.47
		Phonological Memory	91.50 ± 12.85 †	84.70 ± 8.06 †	102.20 ± 14.72
		Rapid Naming	101.75 ± 11.96	89.50 ± 12.10 \$ ‡	106.40 ± 12.92
Language Tests	CELF-3	Receptive Language	95.42 ± 15.83 †	92.50 ± 15.74 †	117.47 ± 19.85
		Expressive Language	97.00 ± 10.39 †	85.30 ± 16.50 †	111.07 ± 17.64
	TLC-E	Ambiguous Sentences	7.92 ± 2.94 †	6.40 ± 2.41 †	10.53 ± 2.90
		Making Inferences	10.00 ± 2.99	8.20 ± 2.82	10.73 ± 1.75
		Figurative Language	8.75 ± 3.33 †	7.30 ± 2.58 †	12.13 ± 2.92

† p < .05, NF-1 and RD vs. Controls

‡ p < .05, RD vs. NF-1

\$ p < .05, RD vs. Controls

We also have presented (or will be presenting) several other findings from data from this grant; see "Reportable Outcomes" for a description (Cutting & Scarborough, 2005; Rimrodt, Lightman, Abel, Denckla, & Cutting, 2005; Rimrodt, Lightman, Roberts, Denckla, & Cutting, 2005)

Problems in Accomplishing Tasks: Over the course of the grant, we had significant problems accomplishing our goals because of difficulties with changing regulations with regard to Human Subjects issues (e.g., the enactment of HIPAA, the shut down of the Johns Hopkins School of Medicine IRB, etc.; see previous reports). However, for the third and fourth years of the grant we had no significant difficulties accomplishing tasks, and had a highly productive ending of the grant in terms of recruiting and testing the number of subjects in that we need to fulfill the goals of the grant.

Recommended Changes: During the course of the grant, we did not encounter any issues that suggested that we should have considered changing our goals/procedures of the grant in any manner.

KEY RESEARCH ACCOMPLISHMENTS

- Identified and established connections with many recruiting sources that ensured the success of the study
- Saw the targeted number of subjects needed for analyses (121 subjects, 93 of which were eligible for the study).
- Entered all neuropsychological data and conducted statistical analyses.
- Presented and published abstracts at the *International Neuropsychological Society*.
- Have a manuscript in preparation regarding the neuropsychological findings between NF-1, RD, and Control groups.
- Wrote an invited article on the learning disabilities present in NF-1 for a special issue of *Learning Disabilities Research and Practice*.
- Collected and analyzed MRSI data for children with NF-1 (from sibling pairs)
- Collected data for 39 children for the fMRI tasks
- Analyzed data on 39 children for the fMRI tasks
- Have a manuscript in preparation regarding the fMRI findings between NF-1, RD, and Control groups.

REPORTABLE OUTCOMES

There are several reportable outcomes that have resulted directly from this grant, including published papers and abstracts on the MRI and neuropsychological findings. Cutting, Koth, David, & Denckla (2003) found that both the NF-1 and RD groups showed lower scores than the control group on measures of reading and language, although the NF-1 group performed higher than the RD group on the reading measures. Unlike children with RD, children with NF-1 did not show impairment on rate of retrieval (Rapid Naming), which tends to be predictive of reading fluency. Cutting, LE, Clements, A., Schafer, J., Pekar, J., Mostofsky, SH, Denckla, MB (2004) found statistically significant differences between RD and controls and NF-1 and controls on the neural circuitry used during a visuospatial task (the JLO). The RD group showed significantly greater activation than controls in the left parietal and right premotor areas, while children with NF-1 showed significantly greater activation than controls in the right basal ganglia (a typical location of T2-weighted hyperintensities found in NF-1) and inferior frontal gyrus. These results suggest that children with NF-1 and RD may utilize different neural mechanisms than controls to perform visuospatial tasks. Cutting, Clements, Lightman, Yerby-Hammack, & Denckla (2004) reviewed the literature on learning disabilities in NF-1 for a special issue of *Learning Disabilities Research & Practice*. A survey of the literature on the cognitive aspects of NF-1 suggests the need for educational intervention studies, which will be the next focus of our research on NF-1 (see below description for grant application). Cutting and Scarborough (2005) will be presenting data on measurement of reading comprehension using data collected from this grant; findings suggest that how reading comprehension is measured is a significant issue, and may help reveal why children with NF-1 show difficulties on particular cognitive tests. In two separate abstracts (Rimrodt, Lightman, Abel, Denckla, & Cutting, 2005; Rimrodt, Lightman, Roberts, Denckla, & Cutting, 2005), we further examined the issue of reading comprehension measurement using data collected from this grant, and again showed that differences exist depending on how reading comprehension is measured, particularly for children who have difficulty with reading

comprehension. This is especially important to consider for children with NF-1, who often have reading comprehension impairments because of their poor language skills.

While not directly resulting from the data collected from this grant, this grant has helped support our overall program of research on NF-1 at the Kennedy Krieger Institute. This includes two published abstracts and three publications. One publication, published in *Neurology*, provides detailed analyses of cortical gray and white matter volumes in males with NF-1; lobar (frontal, occipital, parietal, and temporal lobes) and lobar subdivisions (e.g., prefrontal lobe) areas were measured (Cutting, Cooper, Koth, Mostofsky, Kates, Denckla, & Kaufmann, 2002). Findings showed increase in frontal and parietal white matter volumes in patients with NF-1, and frontal gray matter reductions in males with NF-1 who also had Attention Deficit Hyperactivity Disorder (ADHD). Another publication examined the growth of "spared" and "impaired" cognitive measures in children with NF-1 as compared to their siblings (Cutting, Huang, Zeger, Koth, Denckla, 2001). Findings indicated that over time children with NF-1 do not "catch up" to their siblings on those measures that were "impaired"; furthermore, there were no significant differences in growth rates between children with NF-1 and their siblings for the "spared" and "impaired" cognitive functions. We also have examined the longitudinal evolution of T2-weighted hyperintensities (UBOs; Kraut, Gerring, Cooper, Thompson, Denckla, Kaufmann, 2004). Findings showed that the total number of UBO-occupied locations evolved in a non-linear manner, with a decrease between approximately ages 7-12 years, followed by a progressive increase in adolescence. The same pattern was also found for UBO number and/or volume for all regions, with the exception of cerebellar hemispheres. In addition, we have presented a study examining brain volumes of parietal and frontal lobes and neuropsychological functioning in NF-1 and control groups (Crocetti, Cutting, Koth, David, Kates, & Denckla, 2003). Findings showed an inverse relationship between frontal lobe volumes and the Judgment of Line Orientation test, regardless of group membership. Finally, we presented the results of fMRI of Judgment of Line Orientation comparing adults with children, thereby helping to understand developmental differences in visuospatial functioning in typically developing populations (Cutting, Clements, Schafer, Mostofsky, Pekar, & Denckla, 2004).

We have applied for funding from the National Institutes of Health (NINDS) to continue our work towards understanding the neurological correlates of the language and reading disabilities reported in children with NF-1. Specifically, we are focusing on refining the knowledge of how to treat children with NF-1 who have reading disabilities as compared to children with idiopathic reading disabilities (IRD). For this research, we propose to determine if children with NF-1 who have reading disabilities respond in the same manner, both neurobiologically (by use of fMRI) and neuropsychologically, to educational interventions known to be highly effective for children with IRD. It has been established that specialized educational interventions are highly successful for children with IRD, resulting in not only improved reading abilities, but also "normalization" brain activation during reading tasks (using fMRI). We seek to determine if these same interventions will be as effective for children with NF-1. We received a quite favorable score on this grant (17th percentile), but not quite within the funding cutoff (16th percentile) and will be resubmitting it for July 1, 2005 for re-review.

We applied for and received funding from the National Institutes of Health for a grant entitled "Cognitive and Neural Mechanisms of Reading Comprehension" (PI: Cutting; R01 HD 044073-

01). This grant relates to our understanding of idiopathic reading and language disorders, which is relevant to treating the reading and language disorders prevalent in NF-1.

CONCLUSIONS

We have had significant success in reaching the goals of the grant. We saw 121 children (93 who were eligible), published one paper, and presented numerous abstracts at international meetings. We are currently preparing a manuscript on the neuropsychological results. We also implemented our fMRI paradigms and collected and analyzed fMRI data on 39 children, and are currently preparing a manuscript for publication with this data. Additionally, we have analyzed MRSI data on the sibling pairs that we have seen and will be preparing a manuscript from those findings soon. Therefore, we have been able to address the goals of the grant. Overall, findings suggest that children with NF-1 show similar difficulties as children with RD, with both groups showing weaknesses in reading accuracy (decoding), reading comprehension, receptive and expressive language, and some aspects of inferential language. On the other hand, children with NF-1 appear to have some notable differences from children with RD. Unlike children with RD, results suggest that some aspects of inferential language and rate of retrieval are relatively spared in children with NF-1. These findings indicate that intervention for the associated learning disabilities in children with NF-1 will be able to be tailored to this pattern of strengths and weaknesses (e.g., strong rate of retrieval abilities may help remediate language disabilities). Our fMRI findings also suggest that children with NF-1 show different patterns of activation on both reading and visuospatial tasks, indicating that they use different neural circuitry when processing information. Further work in this area may help reveal how this impacts cognition in NF-1.

This grant has also helped support our overall program of research on NF-1 at the Kennedy Krieger Institute. This includes three publications (one published in *Journal of the International Neuropsychological Society*, one in *Neurology* and another in the *American Journal of Medical Genetics*) and two published abstracts. We have also obtained NIH funding for a R01 on a related topic (reading comprehension difficulty) and had a NF-1 grant on reading intervention that we submitted to NIH reviewed favorably.

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Rimrodt SL, Lightman A, Roberts L, Denckla MB, & Cutting, LE (2005). *Are All Tests of Reading Comprehension the Same?* Presented at the International Neuropsychological Society Meeting, St. Louis, MO.

LIST OF PERSONNEL RECEIVING PAY FROM THE RESEARCH EFFORT

- Amy Clements
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- Martha Denckla
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- Joanna Schafer
- Jeanne Wilkins
- Pamula Yerby-Hammack